

# ***EXHIBIT 7***



## Signal management



A safety signal is information on a new or known adverse event that may be caused by a medicine and requires further investigation. The European Medicines Agency (EMA), together with the regulatory authorities in the Member States and marketing authorisation holders are responsible for detecting and managing safety signals.

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Safety signals can be detected from a **wide range of sources**, such as spontaneous reports, clinical studies and scientific literature. The EudraVigilance database is an important source of information on suspected adverse reactions and signals.

The presence of a safety signal does not directly mean that a medicine has caused the reported adverse event. An illness or another medicine taken by the patient could also be the cause.

The assessment of safety signals establishes whether or not there is a **causal relationship** between the medicine and the reported adverse event.

The evaluation of safety signals is part of routine pharmacovigilance and is essential to ensuring that regulatory authorities have the most up-to-date information on a **medicine's benefits and risks**.

### Also on this topic

- PRAC recommendations on safety signals

### Monitoring EudraVigilance: legal basis and guidance (update)

**Revision of Implementing Regulation (EU) No 520/2012 and termination of the pilot of signal detection in EudraVigilance by Marketing Authorisation Holders (MAHs).**

The Implementing Regulation (EU) No 520/2012 of 19 June 2012 required Marketing Authorisation Holders (MAHs) to continuously monitor the EudraVigilance (EV) database and inform forthwith the Agency and National Competent Authorities (NCAs) of validated signals detected in the database. In 2017, the European Commission (EC) agreed to a pilot phase on the implementation of the above legal requirements. The pilot started on 22 February 2018 with a focus on a limited number of active substances and combinations of active substances ('pilot list'). During this pilot period, only those MAHs with an active substance or combination included on the 'pilot list' had the obligation to perform signal detection in EudraVigilance and follow the above requirements for these substances.

Based on the experience acquired through the pilot since 2018, the requirements for MAHs are currently being updated through an amendment to **the Implementing Regulation (EU) No 520/2012**.

The update of the Implementing Regulation will likely be published in the first half of 2025. Consequently, the pilot on signal detection by MAHs in EV will be **extended beyond the end of 2024 in its current form and will be terminated** as of entry into force of the amended Implementing Regulation (EU).

The requirements established in the updated Implementing Regulation will be applicable to all MAHs with medicinal products authorised in the EEA.

GVP Module IX on Signal Management will be amended in due course to reflect this update. The Agency will continue to support MAHs in their signal management activities. Further information can be found under EudraVigilance training and support.

Guidance on the notification of **emerging safety issues** can be found on the contacts at the EMA page.

EMA has also published **scientific guidance** on screening for adverse reactions in EudraVigilance for use by the Agency, national competent authorities and MAHs. The guidance discusses the methods recommended and implemented in EudraVigilance for screening for adverse reactions:

- Screening for adverse reactions in EudraVigilance

### Member State signal management work-sharing

A **lead Member State** may be appointed to monitor data in EudraVigilance, validate and confirm signals on behalf of the other Member States. This applies to active substances contained in medicinal products authorised nationally in more than one Member State.



#### List of substances and products subject to worksharing for signal management

Reference Number: EMA/563056/2014 Rev. 13

English (EN) (149.91 KB - XLSX)

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For substances with no lead Member State, all Member States have joint responsibility for monitoring those medicines they have authorised.

### Recommendations on signals

The Pharmacovigilance Risk Assessment Committee (PRAC) is responsible for **prioritising and assessing signals** and issuing subsequent recommendations on medicines authorised in the European Union, including nationally and centrally authorised medicines.

The PRAC recommendation may include one or a combination of conclusions, including:

- No need for further evaluation or action at present;
- Need for additional information, including:
  - monitoring any relevant emerging information as it becomes available;
  - additional analysis in EudraVigilance or other data sources;
  - additional data from the [marketing authorisation holder](#) in the next [periodic safety update report](#) (PSUR) or submit an ad-hoc PSUR;
  - a [post-authorisation safety study](#) conducted by the [marketing authorisation holder](#);
- Need for regulatory action, such as:
  - updating of the [product information](#) (summary of product characteristics and package leaflet) and/or [risk management plan](#) through a [variation](#);
  - a [referral procedure](#);
  - urgent safety restrictions.

For more information, see:

[Questions and answers on signal management](#)

[Marketing authorisation holders](#) should monitor [PRAC recommendations on safety signals](#) the Agency publishes on its website and take action accordingly.

As of January 2015, EMA publishes **translations of recommendations** (reviewed by the [national competent authorities](#)) for the updating of product information into all official EU languages plus Norwegian and Icelandic. [Marketing authorisation holders](#) can use these translations to update their [product information](#). This aims to ensure that consistent and clear information is available to patients in a timely manner in all Member States.

## Designated medical events

EMA has developed a list of designated medical events containing **medical conditions** that are inherently **serious** and often medicine-related:

[Designated Medical Event \(DME\) list](#)

It does not address product specific issues or medical conditions with high prevalence in the general population.

The list contains [Medical Dictionary for Regulatory Activities](#) (MedDRA) terms and serves as a **safety net in signal detection**. EMA and Member States use it to focus on reports of suspected adverse reactions that deserve special attention, irrespective of statistical criteria used to prioritise safety reviews.

The designated medical event list is one of the tools the [European medicines regulatory network](#) uses and is **not intended as a comprehensive list** of terms for signal detection activities.

EMA has published the list to ensure its approach is transparent. It is subject to review in light of further experience with its use.

## More information

For more information on signal detection and management in the EU and **regulatory requirements** for [marketing authorisation holders](#), see:

- [Good pharmacovigilance practices](#) (GVP) - see Module IX on signal management

[Questions and answers on signal management](#)

### Related content

- [Pharmacovigilance](#)
- [Good pharmacovigilance practices](#) (GVP)
- [Pharmacovigilance legislation](#)
- [PRAC recommendations on safety signals](#)

### Related documents



#### Questions and answers on signal management

Reference Number: EMA/261758/2013 Rev 4\*

**English (EN)** (336.17 KB - PDF)

First published: 04/10/2013 Last updated: 15/01/2021

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### Related EU legislation

- [Directive 2001/83/EC](#)
- [Regulation \(EC\) No 726/2004](#)
- [Commission Implementing Regulation \(EU\) No 520/2012](#)

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